

**COMPARATIVE BIOAVAILABILITY STUDIES:
REGULAR RELEASE SOLID ORAL DOSAGE FORMS**

Purpose:

This policy outlines criteria to determine the need for comparative bioavailability studies for drug product submissions. Once implemented, the policy may lead to changes which alter the requirements for new products and/or changes to a given existing drug product.

The Therapeutic Products Programme (TPP), Health Canada has undertaken a review and renewal of the drug regulatory system in an effort to revise its focus and improve its efficiency, flexibility and responsiveness. To this end, the TPP is moving towards a Drug Product Licensing Framework II (PLF). As part of the renewal process, the TPP has initiated a re-evaluation and update of the criteria which determine the need for comparative bioavailability studies of drug products for use within the PLF. Revised criteria and a transparent decision process will clarify and facilitate the drug submission process for manufacturers, TPP staff and other stakeholders.

Background:

As the TPP moves towards the proposed PLF with its risk management focus,¹ it is clear that there is a need to re-evaluate the basis upon which the requirement for comparative bioavailability studies is founded. The principle underlying the PLF is that "drugs with potentially high risks will require the highest level of comprehensive pre-market data submission, will receive more intense pre-market scrutiny, and will have a higher level and frequency of post-approval surveillance."² This policy

¹ wherein "risk refers to the available knowledge/experience relating to the quality, safety and efficacy of the drug product and/or identified product safety concerns"

² Therapeutic Products Programme. **Overview of the Product Licensing Framework II.** Ottawa: September 1997.

proposal and the criteria outlined for comparative bioavailability studies herein are consistent with this goal.

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Under the current TPP policy, all subsequent entry drug products which are defined as "new" drugs by the Food and Drugs Act require comparative bioavailability studies. In addition, in 1995 the TPP introduced the "DIN guidelines" which contain criteria that identify which subsequent entry drug products for "old" drugs also require such studies to support their submissions. The proposed PLF (and its four categories, based on levels of risk) replaces the old groupings of drug products; in other words, drug products will no longer be categorized as "new" versus "old."

Under existing TPP policies, responsibility for establishing the safety and efficacy of a drug rests with the manufacturer.^{3,4} In the case of subsequent entry products, this can often be achieved by demonstrating equivalence against the Canadian reference product; that is, to provide evidence that the safety and efficacy profiles of the subsequent entry product are comparable to that of the innovative product which is marketed in Canada and for which safety and efficacy has been demonstrated clinically.⁵

Finally, one of the prime goals in terms of outcomes of the PLF is the creation of an understandable and transparent process that provides clear guidance to process participants, both internal and external. This policy proposal and the attendant criteria are consistent with this goal.

Scope :

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- ³ Therapeutic Products Programme. **Policy: Waiver of Comparative Bioavailability Studies for Oral Solutions.** Ottawa: October 10, 1996.
 - ⁴ Therapeutic Products Programme. **Policy: Bioequivalence of Proportional Formulations - Solid oral dosage forms.** Ottawa: March 7, 1996.
 - ⁵ Therapeutic Products Programme. **Policy: Canadian Reference Product.** Ottawa: December 5, 1995.

This policy defines criteria to be used to determine those conventional-release solid oral drug products entering the Canadian market for which the safety and efficacy may be established on the basis of comparative bioavailability studies against the Canadian reference product. Please note that these criteria make no differentiation between prescription and nonprescription medications; or between products from the "generic" and "innovative" sectors of the industry. These criteria will facilitate the development and maintenance of the Biopharmaceutics List⁶ of the proposed PLF, which relates to **Category III⁷ Subgroup III-5⁸ and Subgroup III-6 Products.**⁹

⁶ Appendix I of the draft PLF II identifies a Biopharmaceutics List which, initially, will be based on: drugs requiring the submission of an Abbreviated New Drug Submission (ANDS); drugs which require comparative bioavailability studies as defined in the Final Report (D-09); Drug Identification Number, September 1994; and, all New Active Substances (NAS) as they receive notice of compliance.

⁷ a drug product for which there is some prior experience of knowledge regarding the safety, efficacy and

quality aspects of the active ingredient(s) of the drug product

⁸ the product is presented for systemic effect in one of the following dosage forms where a pharmaceutically equivalent drug product has been previously licensed for sale in Canada: solid oral dosage form, an oral suspension; a powder or granules for oral suspension, or an oral solution

⁹ the product is contained in combination with one or more other active ingredients where a pharmaceutically equivalent drug product has been previously licensed for sale in Canada

Policy:

With the implementation of the proposed PLF, subsequent-entry drug products will be required to carry out comparative bioavailability studies (assuming that such studies will adequately establish their safety and efficacy), unless they qualify for a waiver from such studies (i.e. safety and efficacy can be established solely on the basis of pharmaceutical equivalence). These requirements are outlined in the **Revised Criteria for Comparative Bioavailability Studies** and the **Algorithm** section of this policy (Appendices I and II, respectively).

Rationale:

There is a need to develop transparent criteria to define which subsequent-entry drug products will require comparative bioavailability studies to establish safety and efficacy. One of the functions of the algorithm proposed is to serve as a risk assessment tool vis-a-vis subsequent-entry drug products; and, thus, to provide a framework for and to improve the transparency of the decision process. An important principle underlying the algorithm is that the onus is on the manufacturer to provide data/information to justify waiver from the requirement for comparative bioavailability studies for a particular product.

The criteria developed are intended to conform to the fundamental principle underlying the proposed PLF; that is, that "drugs with potentially high risks will require the highest level of comprehensive pre-market data submission, will receive more intense pre-market scrutiny and will have a higher level and frequency of post-approval surveillance."

Where there is insufficient information to justify waiver of comparative bioavailability studies, the benefit of the doubt should go to potential consumers of the medication in an effort to minimize their risk.

Appendix I: Revised Criteria for Comparative Bioavailability Studies¹⁰

Decision Points for Determining the Need for Comparative Bioavailability Studies

Introduction:

The following outlines criteria and a transparent decision process which are intended to clarify and facilitate the drug submission process for manufacturers, TPP staff and other stakeholders. These criteria will be used to determine the need for comparative bioavailability studies in demonstrating bioequivalence for subsequent-entry drug product submissions (i.e. whether or not a "biostudy" is required in addition to the data regarding chemistry, manufacturing and dissolution that are required of all submissions). (The issue of what standards must be met once it is decided that a "biostudy" is needed comes under a separate discussion). Once implemented, the policy may lead to changes which alter the requirements for new products and/or changes to a given existing drug product.

*These criteria apply to those conventional-release solid oral drug products entering the Canadian market for which the safety and efficacy may be established on the basis of comparative bioavailability studies against the Canadian reference product. Please note that they make no differentiation between prescription and nonprescription medications; or between products from the "generic" and "innovative" sectors of the industry. The criteria will facilitate the development and maintenance of the Biopharmaceutics List of the proposed PLF, which relates to **Category III Subgroup III-5 and Subgroup III-6 Products**.*

¹⁰ Modified from criteria outlined in: Drugs Programme Guidelines. **Preparation of Drug Identification Number Submissions**. Ottawa: Health Protection Branch, Health Canada (February 22, 1995).

NOTE: In the remainder of this document, these will be referred to as the "**DIN Guidelines**."

A) General Principles

- Demonstration of bioequivalence is **generally** required for solid oral dosage forms (regular formulations with uncomplicated characteristics¹¹, regular release with complicated or variable pharmacokinetics¹², modified release formulations¹³), oral suspensions, powders/granules for oral suspension, and oral solutions intended for systemic effect.¹⁴
- The criteria outlined in C) below focus on requirements for demonstration of bioequivalence via comparative bioavailability studies in regular

¹¹ **Conduct and analysis of bioavailability and bioequivalence studies (1992). Part A: Oral dosage formulations used for systemic effects.** Ottawa: Drugs Programme, Health Protection Branch, Health and Welfare Canada.

NOTE: In the remainder of this document, these guidelines will be referred to as "**Part A.**"

¹² Expert Advisory Committee on Bioavailability. **Draft report on bioavailability of oral dosage formulations of drugs used for systemic effects - Report C: Report on bioavailability of oral dosage formulations, not in modified release form, of drugs used for systemic effects, having complicated or variable pharmacokinetics.** Ottawa: Health Protection Branch, December 1992.

NOTE: In the remainder of this document, these guidelines will be referred to as "**Report C.**"

¹³ **Conduct and analysis of bioavailability and bioequivalence studies (1996). Part B: Oral modified release formulations.** Ottawa: Therapeutic Products Programme, Health Canada.

NOTE: In the remainder of this document, these guidelines will be referred to as "**Part B.**"

¹⁴ Adapted from DIN Guidelines: **Section VII-B Conditions.**

release/conventional oral solid dosage forms; and make no distinction between prescription and non-prescription drug products.

- The purpose of these criteria is to aid in the development of a **Biopharmaceutical List** (under the proposed Drug Product Licensing Framework) which defines active ingredients (chemical substances) for which bioavailability and/or pharmaceutical chemistry problems exist; and, therefore, comparative bioavailability studies are required as part of the licensing submission process.
- These criteria are to be used in conjunction with the decision algorithm provided in Appendix III.

B) Bioequivalence Waivers

A waiver of bioequivalence may be granted if it can be determined that such a study is not necessary (i.e. that pharmaceutical equivalence is adequate), as outlined in the following situations:¹⁵

- 1) For different strength(s) of the same dosage form produced by the same manufacturer, if the product meets all of the following:
 - a) the bioequivalence of one of the strengths to the Canadian reference product has been demonstrated; **and**,
 - b) the composition of the other strength(s) is proportionally similar in its medicinal and non-medicinal ingredients to that strength which underwent the acceptable bioequivalence study;¹⁶ **and**,
 - c) all strengths of the drug product exhibit equivalent dissolution profiles.

Note: A waiver of bioequivalence will not normally be granted for additional strengths of medicinal ingredients with known nonlinear pharmacokinetic characteristics affecting absorption and/or first-pass metabolism.

- 2) Non-absorbable oral preparations; since non-absorbability is a relative term, determination of the bioequivalence requirements will be made on a case-by-case basis.
- 3) Oral solutions, elixirs, syrups or other similar solubilized forms containing the **same medicinal ingredient(s)** in the **same concentration(s)** as the

¹⁵ Adapted from DIN Guidelines: **Section VII-B Conditions: Waiver of Bioequivalence Requirement.**

¹⁶ Therapeutic Products Programme. **Policy: Bioequivalence of Proportional Formulations - Solid oral dosage forms.** Ottawa: March 7, 1996.

Canadian reference product and containing no ingredient known to significantly affect absorption of the medicinal ingredient(s).¹⁷

- 4) Justification provided by the applicant must be based on assessment and elimination of all factors outlined in C) below, founded in strong scientific principles with thorough documentation of data which demonstrate how each criterion does or does not apply to the drug in question. Each justification will be assessed on its own merit. If the required information is unavailable, then a comparative bioavailability study will be required.

¹⁷ Therapeutic Products Programme. **Policy: Waiver of Comparative Bioavailability Studies for Oral Solutions.** Ottawa: October 10, 1996.

- 5) Excluded from the assessment to determine bioequivalence requirements are: homeopathic preparations, traditional herbal medicines and vitamin/mineral/vitamin+mineral preparations.¹⁸

Issues of Note:

- 1) There are situations wherein it is not possible to carry out a comparative bioavailability study (e.g. drug measurement methodology is insufficiently accurate, sensitive or reliable in determining blood concentrations to at least three terminal half-lives [e.g. extremely low blood levels; highly variable blood levels compared to clinical effect; blood levels are meaningless]; or because such methods are not an appropriate means of evaluating the drug product [e.g. non-absorbed products]). In these cases, a comparative pharmacodynamic/clinical study or testing against a reference standard is required.^{3,19}
- 2) Biological drug products are subject to the policies of the Bureau of Biologics and Radiopharmaceuticals.

¹⁸ Adapted from DIN Guidelines: **Section VII-B Conditions: Exclusions.**

¹⁹ Adapted from DIN Guidelines: **Section VII-A 3.b)i).**

C) Absolute Requirements for Comparative Bioavailability Studies^{20,21}

- If any one of the following statements is true for a given drug product, then comparative bioavailability studies must be submitted according to the Drug Product Licensing Framework of the Therapeutics Products Programme.
- These statements attempt to define **known** factors, based on publically available information founded in scientific principles, that a bioavailability problem exists. The inclusion of an issue as a criterion for requiring comparative bioavailability studies is determined based on the impact of that factor on **product** performance and reproducibility issues, as separate from patient performance or reproducibility issues.
- If none of the following statements applies for a given drug product, then the applicant may apply to waive demonstration of bioequivalence [as noted in **B**) above]. A justification for waiver of requirements must be based on scientific

²⁰ Adapted from Part A (see previous footnote) and DIN Guidelines (Appendix E).

²¹ Cartwright AC, Gundert-Remy W, Rauws F, McGilveray I, Salmonson T, Walters S. International Harmonization and Consensus DIA Meeting on Bioavailability and Bioequivalence Testing Requirements and Standards. **Drug Information Journal** 1991;25:471-482.

principles,^{22,23} with the **onus** being on the manufacturer to provide thorough documentation of data to support the application.²⁴ Each justification will be assessed on its own merit. If the required information is unavailable, then a comparative bioavailability study will be necessary.

²² Adapted from DIN Guidelines: **Section VII-A Information Requirements.**

²³ Adapted from DIN Guidelines: **Section VII-B Conditions: Prescription Products.**

²⁴ **Food and Drug Act**, Division 8. August 16, 1995 update.

A drug product requires demonstration of bioequivalence via comparative bioavailability studies if any one of the following conditions pertain:

1) The drug exhibits nonlinear absorption and/or first-pass metabolism in or near the indicated dosing range.

Principle(s) Underlying the Criterion:

This is a new criterion, not originally identified within the existing DIN Guidelines. However, drugs with nonlinear pharmacokinetic properties are identified as an "exception" to the guidelines, methodologies and standards outlined in Part A.

As per Report C, nonlinear pharmacokinetics occur when a change in dose (within the usual dosage range) results in a disproportional change in the concentration of the drug in the blood. Note that for purposes of requiring comparative bioavailability studies, this criterion and the over-riding policy does not include nonlinearity related to drug binding, excretion or biotransformation.

Readers should refer to the TPP draft policy defining bioequivalence standards for drugs exhibiting nonlinear pharmacokinetics;²⁵ as well as other pertinent references regarding how to evaluate bioequivalence in nonlinear drugs.²⁶

Finally, it should be noted that this criterion would include those situations where the drug in question has non-linear characteristics affecting absorption and/or first-pass metabolism; and at the same time is known to form an active metabolite, such that the therapeutic effect was mediated by both the parent compound and the product(s) of metabolism. The TPP policy regarding metabolites and comparative bioavailability studies gives preference to the measurement of the parent drug, because the purpose of

²⁵ Therapeutic Products Programme. **Draft: Bioequivalence requirements: drugs exhibiting non-linear pharmacokinetics.** Ottawa: November 7, 1996.

²⁶ WHO Expert Committee on Specifications for Pharmaceutical Preparations. **Multi-source Pharmaceutical Products: WHO Guideline on registration requirements to establish interchangeability.** Geneva: World Health Organization. February 1, 1995.

comparative studies is to compare formulations. Readers should refer to this policy for further information.²⁷

²⁷ **Policy for Acceptance of Metabolite Data for Comparative Bioavailability Studies.** Ottawa: Therapeutic Products Programme (1996).

References and Supporting Documentation:

Blume HH, Midha KK. Report of Consensus Meeting - Bio-International '92, Conference on Bioavailability, Bioequivalence and Pharmacokinetic Studies. **European Journal of Pharmaceutical Sciences** 1993;1:165-171.

Cartwright AC, Gundert-Remy W, Rauws F, McGilveray I, Salmonson T, Walters S. International Harmonization and Consensus DIA Meeting on Bioavailability and Bioequivalence Testing Requirements and Standards. **Drug Information Journal** 1991;25:471-482.

Jusko WJ. Chapter 2 - Guidelines for Collection and Analysis of Pharmacokinetic Data: Nonlinear Pharmacokinetics. In: Evans WE, Schentag JJ, Jusko WJ, eds. **Applied Pharmacokinetics - Principles of Therapeutic Drug Monitoring**, 3rd edition. Vancouver, WA: Applied Therapeutics, Inc.

Ludden TM. Nonlinear pharmacokinetics: clinical applications. **Clinical Pharmacokinetics** 1991;20(6):429-446.

Marzo A, Balant LP. Bioequivalence: An updated reappraisal addressed to applications of interchangeable multi-source pharmaceutical products. **Arzneimittel-Forschung/Drug Research** 1995;45-1(2):109-115.

2) There is a stereoselective conversion process that affects either absorption or first-pass metabolism (unless it can be demonstrated that there is no such conversion process).

Principle(s) Underlying the Criterion:

This is a new criterion, not originally identified within the existing DIN Guidelines. However, drugs subject to a stereoselective conversion process at the point of absorption and/or first-pass metabolism are identified as an "exception" to the guidelines in Part A.

Draft guidelines are currently under development by the TPP related to specific issues in chiral drug development. These guidelines may take precedent over this criterion when and if they reach the point of implementation.

The degree of stereoconversion must be considered. Karim (see below) discusses the specific situation in which the immediate-release formulation of the drug exhibits significant (>20%) enantiospecific first-pass metabolism of the pharmacologically less-active enantiomer (such that the total drug level is primarily made up of the active enantiomer).

Also to be considered is the requirement under the EU guidelines on chiral drugs,²⁸ specifically as they relate to the use of stereoselective assays for measuring the enantiomers of a racemic mixture in the context of a bioavailability study (i.e. "bioequivalence studies supporting generic applications of chiral medicinal products should be based upon enantiospecific bio-analytical methods, unless: both products contain the same, stable single enantiomer as the active substance, or both products contain the racemate and both enantiomers show linear pharmacokinetics").

References and Supporting Documentation:

Karim A. Enantioselective assays in comparative bioavailability studies of racemic drug formulations: nice to know or need to know? **Journal of Clinical Pharmacology** 1996;36:490-499.

²⁸ CPMP Working party on quality of medicinal products, CPMP Working party on safety of medicinal products, CPMP Working party on efficacy of medicinal products. **EC - Note for guidance: investigation of chiral active substances.** III/3501/91EN, Final, October 1993.

Sarkar MA, Noonan PK, Adams MJ, O'Donnell JP. Pharmacodynamic and pharmacokinetic comparisons to evaluate bioequivalence of atenolol. **Clinical Research and Regulatory Affairs** 1995;12(1):47-62.

Cartwright AC, Gundert-Remy W, Rauws F, McGilveray I, Salmonson T, Walters S. International Harmonization and Consensus DIA Meeting on Bioavailability and Bioequivalence Testing Requirements and Standards. **Drug Information Journal** 1991;25:471-482.

Blume HH, Midha KK. Report of Consensus Meeting - Bio-International '92, Conference on Bioavailability, Bioequivalence and Pharmacokinetic Studies. **European Journal of Pharmaceutical Sciences** 1993;1:165-171.

3) If any one of the constituent ingredients of a combination drug product requires a comparative bioavailability study; or if the rate or extent of absorption of one ingredient affects the pharmacokinetics or pharmacodynamics of the other ingredient(s), then the combination product requires comparative bioavailability studies.

Principle(s) Underlying the Criterion:

This is a new criterion, not originally identified within the existing DIN Guidelines. However, combination drug products are identified as an "exception" to the guidelines in Part A; and are identified as "complicated" drug products in Report C.

Combination drug products (i.e. more than one active ingredient in the formulation) are typically formulated within a single dosage form to take advantage of their additive or synergistic activities. When such additive or synergistic effects occur at the level of absorption or first-pass metabolism, then it is important to ensure that the component products interact consistently with each other within the specific formulation so as not to alter the bioavailability of one or both of the active ingredients in a way that is different from the reference product

References and Supporting Documentation:

Cartwright AC, Gundert-Remy W, Rauws F, McGilveray I, Salmonson T, Walters S. International Harmonization and Consensus DIA Meeting on Bioavailability and Bioequivalence Testing Requirements and Standards. **Drug Information Journal** 1991;25:471-482.

Schran HF, Petryk L, Chang CT, O'Connor R, Gelbert MB. The pharmacokinetics and bioavailability of clemastine and phenylpropanolamine in single-component and combination formulations. **Journal of Clinical Pharmacology** 1996;36:911-922.

4) The drug exerts its indicated therapeutic activity within a narrow therapeutic range.

Principle(s) Underlying the Criterion:

This criterion was originally identified in Report C, and was carried forward in the existing DIN Guidelines. Drugs with a "narrow therapeutic range" are identified as an "exception" to the guidelines in Part A.

More specifically, according to the definition used in Report C, drugs falling under this criterion "commonly exhibit adverse effects which limit the therapeutic use in doses close to those required for the therapeutic effect. When there is a known relationship of plasma concentrations to therapeutic and toxic effects, the ratio of the lowest concentration at which clinical toxicity commonly occurs (toxic) to the median concentration providing a therapeutic effect (therapeutic) would not be greater than 2."

For purposes of this criterion, the therapeutic range refers to the minimum and maximum blood (or other body fluid) concentrations (or laboratory monitoring parameters, e.g. INR for anticoagulants) between which the drug exerts the activity for the indicated therapeutic effect desired. It should be noted that the terms **"therapeutic range and concentration@ are often used synonymously in the literature surrounding this topic. Examples of drugs considered to be narrow therapeutic range products may include but are not limited to: digoxin, theophylline and warfarin.**

The issue of a more specific definition of "narrow therapeutic range" than that outlined in Report C is one which may require further development. This definition then needs to be defined in policy and used consistently therein (i.e. in the TPP policy re: bioequivalence guidance for narrow therapeutic range drugs now in the draft phase). For instance, according the regulations pertaining to the US FDA [i.e. 21 C.F.R. 320.33(c)], narrow therapeutic ratio is defined by the following:

- "a) there is less than a twofold difference in median lethal dose (LD50) and median effective dose (ED50) values, or
- b) there is less than a twofold difference in the minimum toxic concentrations and minimum effective concentrations in the blood, and
- c) safe and effective use of the drug product requires careful titration and patient monitoring"

References and Supporting Documentation:

Anon. FDA position on product selection for "narrow therapeutic index" drugs. **Am J Health-Syst Pharm** 1997;54:1630-2.

Benet LZ, Goyan JE. Bioequivalence and narrow therapeutic index drugs. **Pharmacotherapy** 1995;15(4):433-440.

Pang DC. Drugs with a narrow therapeutic index. **AAPS Newsletter** 1997;December:10-13.

5) The drug exhibits a steep dose-response curve.
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Principle(s) Underlying the Criterion:

This is a new criterion, not originally identified within the existing DIN Guidelines. However, the Canadian Reference Product policy does identify an “uncomplicated” drug as one which does not exhibit “a steep dose/response relationship” (i.e. if it does, then it is a “complicated” drug product).

A drug product is said to have a “steep dose-response curve” if small changes in the formulation (and, thus, the dose delivered and, therefore, the systemic concentration) of the drug lead to significant changes in pharmacodynamic response (i.e. effect).

This criterion is distinct from that regarding drugs with a “narrow therapeutic range.” It is not only important to ensure bioequivalence in terms of a given concentration range; but in some cases it is also the rate of concentration change that may be characteristic of a drug and its formulation which may be important to outcomes.

References and Supporting Documentation:

6) The drug exhibits concentration-dependent toxicity within the recommended dosing range.
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Principle(s) Underlying the Criterion:

This is a new criterion, not originally identified within the existing DIN Guidelines. However, drugs with "high toxicity" are identified as an "exception" to the guidelines in Part A. In addition, the criteria in the Canadian Reference Product policy identify an "uncomplicated" drug as one which does not exhibit "a risk of serious undesired effects" (i.e. if the drug does exhibit such characteristics, then it is a "complicated" drug product). Thus, it is important to ensure comparability of effect for such high-risk drugs, even if the effect is a "toxic" one.

As noted in Report C, a highly toxic drug is "one whose therapeutic use may result in dose- or concentration dependent adverse effects, which are persistent, irreversible or slowly-reversible, or life-threatening."

While some may consider toxicity to be a "patient" factor, the formulation of a given drug product may influence the amount of drug release which, in turn, is a determinant of toxicity. **Examples of drugs considered to be highly toxic products may include but are not limited to: antineoplastic medications.**

Finally, a highly toxic drug is not necessarily a drug with a "narrow therapeutic range," as the former may exert toxicity within a normal therapeutic concentration or recommended dosing range which may be quite wide. Thus, it is important to capture this factor as a separate criterion.

References and Supporting Documentation:

7) To assure safe and effective drug therapy, the drug requires careful dosage titration and patient monitoring based on drug concentration measurements.

Principle(s) Underlying the Criterion:

This criterion was originally identified within the existing DIN guidelines, and applies to drugs wherein the concentration of the drug in blood (or other body fluids) needs to be tailored to the individual clinical needs of the patient. Such drug products may or may not be "narrow therapeutic range" or "highly toxic" drugs.

For these drugs, specific drug concentrations are required in a given individual to ensure therapeutic efficacy. As a result, greater assurance of comparable plasma drug concentrations is required if there is potential for two products to be switched in the individual who has been stabilized in the absence of medical supervision.

The principle enacted through this criterion is the need to ensure comparable plasma levels when switching from one drug product to another when a patient is stabilized at a given drug concentration. **Examples of drugs requiring dosage titration and patient monitoring based on drug concentration measurements may include but are not limited to: phenytoin and theophylline.**

While the concept of therapeutic drug monitoring and drug concentration measurement may be embodied in or overlap with other criteria listed herein, it is felt that it is important to keep this as a separate criterion for products not captured by the "narrow therapeutic index" criterion, the "high toxicity" criterion and/or the "steep dose response curve" criterion.

References and Supporting Documentation:

Pang DC. Drugs with a narrow therapeutic index. **AAPS Newsletter** 1997;December:10-13.

8) There is pharmacokinetic evidence that:

a) absorption is transit time dependent because the drug is associated with site-specific absorption
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Principle(s) Underlying the Criterion:

This criterion was originally identified within the existing DIN guidelines and applies to drug products which are absorbed in a particular segment of the gastrointestinal tract or from a localized site. The Canadian Reference Product policy refers to an "uncomplicated" drug product as one which does not exhibit "an absorption window, i.e. site-specific absorption" (i.e. if it does, then it is a "complicated" drug product).

This is a drug product specific issue that needs to be taken into account in comparative bioavailability studies because of the fact that changes in gastrointestinal dissolution would affect absorption and, thus, have an important impact.

References and Supporting Documentation:

Wacher VJ, Salphati L, Benet LZ. Active secretion and enterocytic drug metabolism barriers to drug absorption. **Advanced Drug Delivery Reviews** 1996;20:99-112.

b) the degree of absorption of the drug is less than 70% compared to V dose.
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Principle(s) Underlying the Criterion:

This criterion was originally identified within the existing DIN guidelines; and is also referred to in Part A, which identifies a drug with “little or no absorption with activity exerted locally in the gastrointestinal tract” as one which is not covered by those guidelines. Finally, the Canadian Reference Product policy refers to an “uncomplicated” drug as one which does not exhibit “variable or incomplete absorption” (i.e. if it does, then it is a “complicated” drug product).

It should be noted that this criterion relates to the F_{abs} ; that is, bioavailability in terms of the amount of drug absorbed and reaching the systemic circulation.

This may include a drug product which is subject to a substantial first-pass effect (i.e. via metabolizing organs [e.g. intestinal wall, liver, portal blood]) within the therapeutic dosing range, such that the therapeutic effect and/or toxicity of the drug product is determined by the rate as well as the degree of absorption.

References and Supporting Documentation:

Aungst BJ. Novel formulation strategies for improving oral bioavailability of drugs with poor membrane permeation or presystemic metabolism. **Journal of Pharmaceutical Sciences** 1993;82(10):979-987.

Benet LZ, Wu CY, Hebert MF, Wachter VJ. Intestinal drug metabolism and antitransport processes: a potential paradigm shift in oral drug delivery. **Journal of Controlled Release** 1996;39:139-143.

c) the drug product is formulated to produce the early onset of an effect, which is critical to the desired therapeutic outcome.

Principle(s) Underlying the Criterion:

This criterion was originally identified within the existing DIN guidelines, and applies to drug products wherein the time of effect is critical to the well-being of the patient and is an integral component of the indication for which the drug product has been formulated.

Drugs with "an important time of effect or rate of absorption" are identified as an exception to Part A. In addition, Report C identifies this group of drugs as "complicated," defining drug products in this category as "one(s) in which the time of onset of effect is important because of therapeutic or toxic effects."

The issue of a more specific definition of "early onset of effect" as it relates to desired outcome is one which may require further development. This definition then needs to be defined in policy and used consistently therein. (For instance, the USP defines "rapid release" or "rapid dissolution" as that which occurs within 10 to 15 minutes for immediate-release dosage forms, using the methodologies defined in the USP monograph for a specific drug product. However, there is no linkage to outcomes *per se*). Further development of such a definition may ultimately lead to the conclusion that such drug products are more appropriately compared based on pharmacodynamic rather than pharmacokinetic studies.

Drug products referred to as "tablet triturates," "buccal tablets," or "sublingual tablets" may fall under this criterion.

References and Supporting Documentation:

Chapter 1088 - In vitro and in vivo evaluation of dosage forms. **USP 23 - The United States Pharmacopeia** (1995). Rockville, MD: United States Pharmacopeial Convention, Inc. p. 1924.

Chapter 1151 - Pharmaceutical dosage forms: Tablets. **USP 23 - The United States Pharmacopeia** (1995). Rockville, MD: United States Pharmacopeial Convention, Inc. pp. 1949-50.

d) the drug is unstable in portions of the gastrointestinal tract.
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Principle(s) Underlying the Criterion:

This criterion was originally identified within the existing DIN guidelines, and applies to drug products wherein the stability of the drug in various parts of the gastrointestinal system may impact on the degree of absorption and, thus, bioavailability.

The acid environment of the stomach and upper segments of the small intestine is usually the area of most concern as related to the issues raised under this criterion.

It should be noted that drug products which incorporate buffers, enteric coatings and film coatings are, by definition, modified-release products. Reference should be made to the appropriate guideline (i.e. Part B) for further delineation of the issues related to these drug products.

References and Supporting Documentation:

- 9) **There is physicochemical evidence that the drug has a low solubility in water (e.g. < 1%), thus limiting its dissolution; or that the volume of gastric fluids required to dissolve the recommended dose greatly exceeds the volume of fluids present in the stomach (i.e. > 100 mL for adults; prorated for infants and children):**

Principle(s) Underlying the Criterion:

This criterion was originally identified within the existing DIN guidelines, and applies to drug products wherein the characteristic of low solubility may impact on the degree of absorption and, thus, bioavailability.

The particle size and/or surface area of the drug product is/are a particularly critical factor(s) in determining dissolution, absorption and, therefore, bioavailability. In addition, certain physical structural characteristics may also lead to poor dissolution and, thus, affect absorption (e.g. polymorphic forms, solvates, solvates, complexes and crystal modifications).

It should be noted that there is some variability in the terminology and/or definitions used in describing solubilities: from "slightly soluble" to "very slightly soluble" to "practically insoluble or insoluble." (For instance, FDA states that highly soluble drugs are those with a dose/solubility volume of less than or equal to 250mL.)²⁹ The TPP reserves the right to reconsider the definition of solubility which will be applied for purposes of this criterion as new information becomes available.

²⁹ Solubility is calculated based on the minimum concentration of drug (mg/mL), in the largest dosage strength, determined in the physiological pH range (pH 1-8) and at a temperature of $37 \pm 0.5^\circ \text{C}$.

Rudman A, Williams RL. Guidance for Industry: Immediate Research Solid Oral Dosage Forms - Scale-up and Post-approval Changes: Chemistry, Manufacturing, and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation (SUPAC-IR). Rockville, MD: US Department of Health and Human Services, Food and Drug Administration, Centre for Drug Evaluation and Research (CDER), November 1995 (CMC 5).

References and Supporting Documentation:

Abdou HM. Chapter 34 - Dissolution. In: **Remington: The Science and Practice of Pharmacy**, 19th ed. Easton, Pennsylvania: Mack Publishing Company. 1995.

Benet LZ, Kroetz DL, Sheiner LB. Chapter 1 - Pharmacokinetics: The dynamics of drug absorption, distribution and elimination. In: **Goodman and Gilman's The Therapeutic Basis of Drugs**. New York: McGraw-Hill. 1996.

Constantinides PP. Lipid microemulsions for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects. **Pharmaceutical Research** 1995;12(11):1561-1572.

DiSanto AR. Chapter 35 - Bioavailability and Bioequivalency Testing. In: **Remington: The Science and Practice of Pharmacy**, 19th ed. Easton, Pennsylvania: Mack Publishing Company. 1995.

Humberton AJ, Charman WN. Lipid-based vehicles for the oral delivery of poorly water soluble drugs. **Advanced Drug Delivery Reviews** 1997;25:103-128.

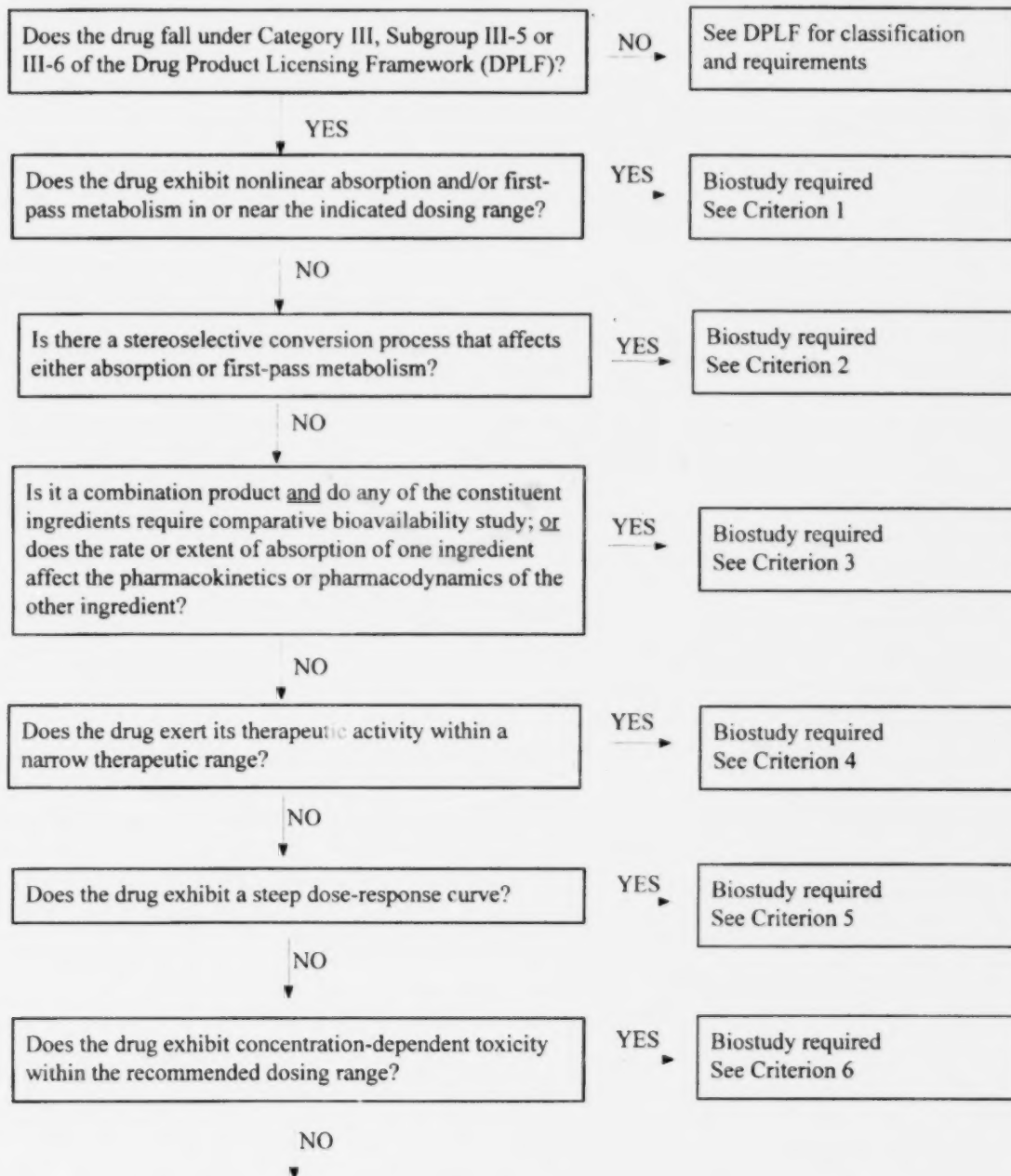
Pouton CW. Formulation of self-emulsifying drug delivery systems. **Advanced Drug Delivery Reviews** 1997;25:47-58.

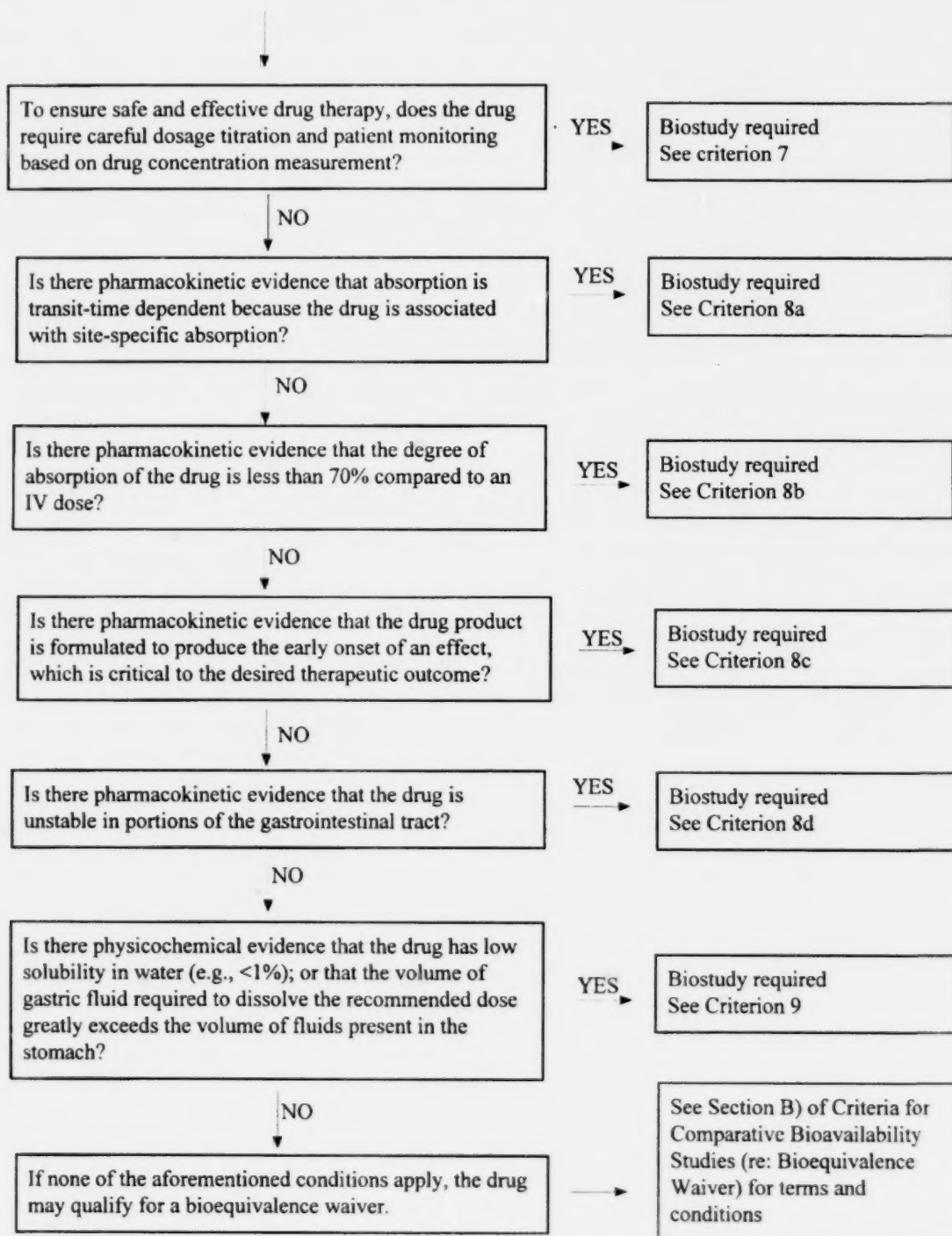
USP 23 - The United States Pharmacopeia. (1995). Rockville, MD: United States Pharmacopeial Convention, Inc. p.10.

Chapter 1151 - Pharmaceutical dosage forms: bioavailability. **USP 23 - The United States Pharmacopeia** (1995). Rockville, MD: United States Pharmacopeial Convention, Inc. p. 1940.

Appendix II: Decision Algorithm for Comparative Bioavailability Studies

DRAFT 31/3/98





Glossary of Terms:³⁰

Adverse Drug Reaction - An undesirable effect that is suspected to be associated with the use of a drug by a subject.

AUC (area under the curve) - The area under the drug (or metabolite) concentration in plasma (or serum, or whole blood) versus time curve. The AUC symbol may be qualified by a specific time (e.g., 8 hours, or AUC₈), time of last quantifiable concentration (AUC_T), or infinity (AUC_I)

Bioavailability - The rate and extent of absorption of a drug into the systemic circulation.³¹ Assessed by serial measurements of drug/metabolites/both in the systemic circulation, to provide a concentration-time curve in order to determine the AUC, C_{max}, and t_{max}.

Bioequivalence - A high degree of similarity in the bioavailabilities of two pharmaceutical products (of the same galenic form) from the same molar dose, that are unlikely to produce clinically relevant differences in therapeutic effects, or adverse

³⁰ Adapted from: **Conduct and analysis of bioavailability and bioequivalence studies (1992). Part A: Oral dosage formulations used for systemic effects.** Ottawa: Therapeutic Products Programme, Health Canada.

³¹ **Conduct and analysis of bioavailability and bioequivalence studies (1996). Part B: Oral modified release formulations.** Ottawa: Therapeutic Products Programme, Health Canada.

effects, or both^{32,33} when administered to patients under conditions specified in the labelling.

³² FIP Consensus Workshop. Is there a need for more precise definitions of bioavailability? **European Journal of Clinical Pharmacology** 1991;40:123-126.

³³ WHO Expert Committee on Specifications for Pharmaceutical Preparations. **Multi-source Pharmaceutical Products: WHO Guideline on registration requirements to establish interchangeability**. Geneva: World Health Organization. February 1, 1995.

Bioequivalent means that test and reference products containing an identical drug or drugs, after comparison in an appropriate bioavailability study, were found to meet the standards for rate and extent of absorption specified in a set of guidelines.^{34,35}

C_{max} (maximum observed concentration) - The observed maximum or peak concentration of a drug (or metabolite) in plasma (or serum, or whole blood).

Excipient - Any ingredient, excluding the drug substances, incorporated in a formulation for the purpose of enhancing stability, usefulness or elegance, or facilitating preparation; for example, base, carrier, coating, colour, flavour, preservative, stabilizer, and vehicle.

First-pass (or Pre-systemic) Metabolism - The metabolism of an orally administered drug occurring during its first pass through certain metabolizing organs, before reaching the systemic circulation. Although the major site of first-pass metabolism is the liver, it may also occur in the intestine or portal blood owing to the presence of enzymes (e.g., esterases). First-pass metabolism is usually assessed by comparing areas under the curve obtained following the oral and intravenous doses of the drug.

Formulation - An ingredient or mixture of specific ingredients; that is, drug substances and excipients in specific amounts, defining a given product.

HPB - Health Protection Branch

Modified-release Dosage Form - A dosage form for which the drug release characteristics of "time course" or "drug release location" are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms.

NOC - Notice of Compliance

³⁴ Pabst G, Jaeger H. Review of methods and criteria for the evaluation of bioequivalence studies. *Eur J Clin Pharmacol* 1990;38:5-10.

³⁵ Chapter 1090 - In vivo bioequivalence guidance: statistical procedures for bioequivalence studies using a standard two-treatment crossover design. **USP 23 - The United States Pharmacopeia** (1995). Rockville, MD: United States Pharmacopeial Convention, Inc. p.1929.

Non-linear Kinetics - A general term referring to dose or time dependency in pharmacokinetic parameters arising from factors associated with absorption, first-pass metabolism, binding, and excretion.

Pro-drug - An inactive (or much less active) precursor that is bio-transformed to the active drug.

Rate of Absorption - The rate at which a drug reaches the systemic circulation after oral administration.

Reference Product - Under the Food and Drugs Regulations (Section C.08.002.1), a Canadian reference product is:

- a) a drug in respect of which a notice of compliance has been issued pursuant to section C.08.004 and which is marketed in Canada by the innovator of the drug,
- b) a drug, acceptable to the Minister, that can be used for the purpose of demonstrating bioequivalence on the basis of pharmaceutical and, where applicable, bioavailability characteristics, where a drug in respect of which a notice of compliance has been issued pursuant to section C.08.004 cannot be used for that purpose because it is no longer marketed in Canada, or
- b) a drug, acceptable to the Minister, that can be used for the purpose of demonstrating bioequivalence on the basis of pharmaceutical and, where applicable, bioavailability characteristics, in comparison to a drug referred to in paragraph a).

For purposes of bioequivalence studies, the reference product is a drug product that has been issued an NOC and is currently marketed in Canada by the innovator; or, a drug product that is acceptable to the Director (TPP).

Time of Maximum Observed Concentration (t_{max}) - The time after administration of the drug at which C_{max} is observed.

TPP - Therapeutic Products Programme



Health Canada / Santé Canada

Therapeutic Products Programme /

Programme des produits thérapeutiques

Tunney's Pasture / Pré Tunney

A.L. / L.A. # 0702A

OTTAWA (Ontario)

K1A 0L2

June 17, 1998 / Le 17 juin 1998

98-018489

To: Associations

Aux : Associations

Re: Comparative Bioavailability Studies
and Drug Product
Licensing

Objet : Études de bio-
disponibilité
comparative et
homologation
des médicaments

As you may be aware, the Therapeutic Products Programme (TPP), Health Canada, has undertaken a review and renewal of the drug regulatory system in an effort to revise its focus and improve its efficiency, flexibility and responsiveness. To this end, the TPP is moving towards a Product Licensing Framework (PLF).

Le Programme des produits thérapeutiques (PPT) de Santé Canada a entrepris, comme vous le savez peut-être, l'examen et le renouvellement du système de réglementation pharmaceutique en vue d'en revoir l'orientation et d'en accroître l'efficacité, la souplesse et la sensibilité. À cette fin, le PPT se dirige vers l'adoption d'un cadre d'homologation des médicaments.

The focus of the new PLF is risk management, that is,

L'accent du nouveau cadre d'homologation est mis sur

drugs with potentially high risks will require the highest level of comprehensive pre-market data submission, will receive more intense pre-market scrutiny, and will have a higher level and frequency of post-approval surveillance. One aspect of the proposed PLF is the development of a "Biopharmaceuticals List" to identify those drugs for which in vitro testing alone is not enough to establish bioequivalence. Please note that these criteria will apply to subsequent-entry products from both innovative and generic manufacturers. To this end, a set of criteria is being developed which relate to the formulation and physicochemical characteristics of a drug product, as well as the pharmacokinetic and pharmacodynamic characteristics of the drug, which may contribute to differences in bioavailability, and hence in safety and efficacy. Drugs meeting these criteria will require the conduct of appropriate comparative bioavailability studies prior to marketing.

la gestion des risques, puisqu'elle prévoit que les produits pharmaceutiques qui ont le potentiel de poser des risques élevés exigeront la présentation des données la plus exhaustive et du plus haut niveau avant leur mise sur le marché, feront l'objet d'une attention du plus haut niveau avant leur mise sur le marché et feront l'objet d'une surveillance plus rigoureuse et plus fréquente après leur mise sur le marché. L'un des aspects du cadre d'homologation proposé est l'élaboration d'une liste de produits biopharmaceutiques identifiant les médicaments pour lesquels les épreuves in vitro ne suffisent pas à établir la biodisponibilité. Veuillez noter que ces critères s'appliqueront aux produits de commercialisation subséquente provenant de fabricants de produits novateurs et de produits génériques. À cette fin, nous sommes à élaborer un ensemble de critères qui se rapporte à la formulation et aux caractéristiques physico-chimiques d'un médicament ainsi qu'aux

caractéristiques pharmacocinétiques et pharmacodynamiques du médicament, qui peuvent contribuer à des différences quant à la biodisponibilité et, par conséquent, à l'innocuité et à l'efficacité des médicaments. Les médicaments satisfaisant à ces critères devront faire l'objet d'étude de biodisponibilité comparative avant d'être mis en marché.

Please find attached a consultant's report which proposes criteria for use in identifying drugs of this type. These draft criteria were developed with the input of BPA staff and the TPP External Working Group on Bioavailability. They are now being submitted to you for comments and suggestions.

Your comments on this draft which may be found at <http://www.hc-sc.gc.ca/hpb-dgps/therapeut/drhtmeng/policy.html#draft/Dpl-cb52.wpd> and its related material are requested by September 1st, 1998. The TPP will consider any comments

Vous trouverez ci-joint le rapport d'un expert-conseil qui propose des critères à utiliser dans l'identification de médicaments de ce type. Ces critères ont été élaborés avec la participation du personnel du BEPP et du groupe de travail externe du PPT sur la biodiversité. Nous vous les soumettons maintenant pour recueillir vos observations et vos suggestions.

Nous vous demandons de nous faire parvenir pour le 1^{er} septembre 1998 vos commentaires sur cette ébauche, qui se trouve à <http://www.hc-sc.gc.ca/hpb-dgps/therapeut/drhtmeng/policy.html#draft/Dpl-cb52.wpd>, et sur les

received in the finaliza-
tion of the criteria and
the attendant policy.

If you have any questions,
please do not hesitate to
contact:

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sc.gc.ca.

documents connexes. Lors-
qu'il mettra la dernière
main à la rédaction des
critères et de la politi-
que, le PPT tiendra compte
de tous les commentaires
reçus.

Si vous avez des questions,
n'hésitez pas à communiquer
avec :

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Original signed by / Original signé par

Dann M. Michols
Director General /Directeur général

Attachment
cc: PMC / CGP

Pièce jointe